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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/643,595	08/22/2000	Emilio Barbera-Guillem	B-29	1027

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BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP
ATTN: IP DEPARTMENT DOCKET CLERK
2300 BP TOWER
200 PUBLIC SQUARE
CLEVELAND, OH 44114

EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/643,595	BARBERA-GUILLEM ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 1/7/03 (Paper No. 12), is acknowledged.
Claims 18-21 have been added.
Claims 1, 6, 10 and 14 have been amended.
Claims 1-21 are pending.

2. Newly submitted amended claims 1, 6, 10 and 14 are directed to multiple species that are patentably distinct from the originally claimed species of an anti-CD20 antibody for the following reasons: newly submitted amended claims 1, 6, 10 and 14 now recite the species of antibodies to CD19, CD21, CD22 and Lym-1, in addition to the species of an anti-CD20 originally claimed (e.g., claim 3). Each antibody is structurally distinct, and therefore a method comprising administering each antibody is patentably distinct.

Since applicant has received an action on the merits for the originally presented species of anti-CD20, this species has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claims 1-21 are under consideration only with respect to the species of an anti-CD20 antibody. See 37 CFR 1.142(b) and MPEP § 821.03.

3. This Office Action will be in response to applicant's arguments, filed 1/7/03 (Paper No. 12). The rejections of record can be found in the previous Office Action (Paper No. 10).

It is noted that New Grounds of Rejection are set forth herein.

Claim Objections

4. Claims 1, 6, 10 and 14 are objected to for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

35 USC § 112 second paragraph

5. Applicant's amendment, filed 1/7/03, has obviated the previous rejection of claims 1-2, 4-7, 9-11, 13-15 and 17 under 35 U.S.C. 112, first paragraph, written description, by limiting the claims to specific antibodies.

35 U.S.C. § 102

6. Applicant's amendment, filed 1/7/03, has obviated the previous rejection of claims 1-2, 4-5, 10-11, 13-15 and 17 under 35 U.S.C. 102(e) as being anticipated by Hale et al (US Pat. No. 6,120,766, of record) by limiting the claims to particular species of antibodies that do not encompass an antibody to CDw52.

7. Applicant's amendment, filed 1/7/03, has obviated the previous rejection of claims 1-2, 4-5, 10-11, 13-15 and 17 under 35 U.S.C. 102(e) as being anticipated by Aruffo et al (US Pat. No. 6,051,228, of record) by limiting the claims to particular species of antibodies that do not encompass an antibody to CD40.

Claim Rejections – 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turk et al. (US Pat. No. 5,958,409, or record) in view of Genain and Hauser (J. Mol. Med. 1997 75:187-197, of record) and Anderson et al. (US Pat. No. 5,776,456, IDS).

Applicant's arguments, filed 1/7/03, have been fully considered but have not been found convincing, essentially for the reasons of record set forth in Paper No. 10.

Applicant's arguments are addressed following a reiteration of the rejection of record in Paper No. 10, as applied to the amended and newly added claims.

The claims are still drawn to a method for reducing a pro-MS immune response, or for treating an individual having MS and a pro-MS immune response or a pro-MS immune response by administering an affinity ligand for a B cell determinant that depletes the targeted nonmalignant B cells, including an affinity ligand that is a chimeric anti-CD20 antibody.

As previously noted, Turk et al. teach and claim a method for treating multiple sclerosis (MS) by administering a therapeutically effective amount of a composition comprising an affinity ligand that is a chimeric antibody that binds the cytokine TNF-α (see entire document, including claims).
Turk et al. also teach

administering a composition comprising the chimeric antibody in combination with a pharmaceutically acceptable carrier (e.g., claim 3 and bridging paragraph of columns 4 and 5);

administering the composition

in a site-directed method directly to the central nervous system (e.g., claims 4 and 5), or by intravenous (i.e., parenteral) injection (e.g. column 7, especially lines 1-15);

further administering an additional component including a chemotherapeutic, anti-inflammatory, or cytolytic agent (e.g., column 7, especially lines 50-56).

Turk et al. also teach that although TNF-α has been implicated as an important effector molecule in MS, other mediators are also important in producing the CNS pathology observed in MS (e.g. columns 2-3 and 7-8). Turk et al. exemplify treatment of EAE (an animal model of MS), in the chronic-relapsing mouse model developed in Biozzi AB/H mice (see Examples, e.g., description of mouse model at column 9).

Turk et al. do not teach administering a composition comprising an affinity ligand that binds a determinant on B cells and effects B cells depletion, such as a chimeric anti-CD20 antibody.

As also previously discussed, Genain and Hauser teach that production of the fully demyelinating lesion of MS involves the interaction of encephalitogenic T cells, proinflammatory cytokines such as TNF-α, and pathogenic antibody (see entire document, e.g., as summarized in the Discussion on page 195). Genain and Hauser review the contribution of the many animals EAE models of MS and their invaluable contributions to understanding the basic immunological mechanisms that underlie autoimmune inflammatory disease of the nervous system (see entire document, e.g., "Introduction").

Genain and Hauser note, however, that the previously established EAE models of MS have failed to provide a reliable indication that a therapeutic successful in EAE will also be successful in the treatment of MS. Genain and Hauser further discuss that important differences exist between previously established models of EAE and MS in terms of pathology, and that in forms of acute EAE inflammation predominates over demyelination, whereas acute demyelination is the pathological hallmark of the early MS lesion (e.g., page 188, left column).

Genain and Hauser present a marmoset model of MS and discuss the advantages of the marmoset model compared to the more widely used rodent models, noting in particular that the marmoset model is novel compared to the rodent models because it develops a relapsing-remitting form of EAE that is characterized clinically by moderate signs of neurological dysfunction and pathologically by early and prominent demyelination accompanied by macrophage infiltration and gliosis, all features of human MS (see especially pages 188-189).

Genain and Hauser also teach that in the marmoset model, like some (but not all rodent models), demyelinating EAE occurs when encephalitogenic T cells act in synergy with pathogenic antibodies (see especially page 188, rt column top and page 193-194). Genain and Hauser conclude that the demonstration of an antibody-mediated component for CNS autoimmune disease, both in the newly developed marmoset as well as certain rodent models, have fundamental implications for the design of future therapies in human MS (page 194, paragraph bridging columns).

Genain and Hauser summarize in Figure 6 that the pathogenesis of the MS-like lesions in the marmoset involve both inflammation involving a T cell component, and a demyelination involving antibody. One of ordinary skill in the art would immediately recognize in view of the teachings of Genain and Hauser that B cells, which were well known in the art to be the source of antibody, thus represent a therapeutic target for the treatment of MS.

As also previously noted, Anderson et al. teach the production of a chimeric anti-CD20 antibody and the use of this antibody to deplete nonmalignant B cells *in vivo* (see entire document, especially Examples II and III on pages 27-page 37). Anderson et al. also teach that CD20 is expressed early in B cell development and remains until plasma cell differentiation (e.g., page 8, 2nd full paragraph).

Given these teachings, the ordinary artisan at the time the invention was made would have been motivated to combine or substitute a method of B cell depletion to reduce or eliminate autoantibody production with the method of treating MS taught by Turk et al. Turk et al. teach using an anti-inflammatory anti-TNF-α chimeric antibody in combination therapies that target other aspects of the MS autoimmune process. Genain and Hauser clearly identify antibodies to be an important component of pathogenesis in the marmoset model, and note that similar findings have been observed in some of the rodent models.

The Examiner previously noted that the Biozzi AB/H mice, which are the model system used by Turk et al., were known in the art to develop chronic-relapsing, rather than acute, EAE; and further notes that Biozzi AB/H (i.e., Biozzi AntiBody/High) mice were known in the art to be more susceptible to EAE induction than Biozzi AB/L (i.e., Biozzi AntiBody/Low) mice, as referenced in the teachings of Turk et al. at column 9, lines 45-51.

Given the clear direction provided by Genain and Hauser that antibody is central to mediating the demyelination found in marmoset EAE, and possibly some rodent models, and that the marmoset EAE model is novel in that it is a particularly representative animal model of MS in terms of the pathology that develops; the ordinary artisan would have had a reasonable expectation that depletion of the B cells that produce the pathogenic antibodies would reduce the demyelination associated with MS and certain EAE models.

Anderson et al. teach that a chimeric anti-CD20 antibody efficiently depletes B cells *in vivo*; and given the expression of CD20 throughout B cell development the ordinary artisan would have reasonably expected that anti-CD20 therapy would deplete mature and memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells and $CD19^+CD5^+sTn^+$ B cells, including nonmalignant B cells when administered to an individual with MS. Irrespective of whether or not a "pro-MS immune response" as defined in the specification on pages 15-16 was tested for in individuals with MS, targeting the pan B cell antigen CD20 would lead to a depletion of B cells irrespective of Ig specificity, and so would necessarily deplete B cells expressing immunoglobulins specific for antigens comprising a terminal alpha 2,6 linked sialic acid.

Thus given the teachings of Genain and Hauser identifying antibody produced by B cells as a primary therapeutic target in MS, the teachings of Anderson et al. that a chimeric anti-CD20 antibody depletes B cells in vivo, and the teachings of Turk et al. that a chimeric anti-TNFα antibody should be used in combination with other agents that target other aspects of the MS autoimmune process; the ordinary artisan at the time the invention was made would have been motivated to substitute or combine the chimeric anti-CD20 antibody of Anderson et al. with the chimeric anti-TNFα antibody of Turk et al. in a method of treating individuals with MS, including administering the combination of antibodies both intravenously (i.e., parenteral) and intrathecally (i.e., in a site-directed manner by delivery into an access that directly supplies the central nervous system).

The ordinary artisan at the time the invention was made would have been motivated in particular to combine the antibodies of Anderson et al. and Turk et al. to target multiple components of the MS immune response with an expectation that the combined therapy would be more efficacious than the single therapy approach. Alternatively, the ordinary artisan would administer only the chimeric anti-CD20 antibody of Anderson et al. during phases of remission in order to maintain depletion of B cells.

Newly added claims 18-21 require that the administered antibody be a monoclonal antibody. However, this limitation is met by the teachings of record since the chimeric anti-CD20 antibody is a monoclonal antibody. Similarly, the newly added limitation that the immune response is in a human does not affect the rejection of record since MS is a disease of humans and the art of record clearly addresses treatment of humans. The Examiner therefore maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments set forth in the Response filed 1/7/03 elaborate on arguments made previously (filed 9/24/01) and addressed by the Examiner in Paper No. 10.

The Examiner's comments may be found in full in Paper No. 10, are incorporated herein by reference. Selective comments are reiterated or elaborated upon below to address Applicant's arguments set forth in the Response filed 1/7/03.

Applicant again contends that the marmoset EAE model of Genain and Hauser is not a "standard model" of EAE and suggests that the Examiner has not rebutted Applicant's previous arguments regarding previous mouse models of EAE. Applicant also argues that Genain and Hauser "teach away" from targeting B cells in MS because MS involves acute demyelination.

It is believed that this comment has been fully addressed in Paper No. 10. In brief, findings in mouse models of EAE do not preclude the acceptance by the ordinary artisan of findings in other models of EAE with respect to the pathogenesis of human MS. Genain and Hauser clearly acknowledge that mouse models of EAE have provided valuable information regarding the antigens involved (e.g. Introduction). However, Genain and Hauser note that pathologically, the marmoset is novel in that it better represents the pathological features of human MS. Thus the Examiner maintains that one of ordinary skill in the art would not consider mouse studies to be a teaching away from role of B cells in MS because the data in different models conflict, and the models that better represent the pathology of human MS clearly indicate a role for antibody in the demyelinating pathology observed in MS and thus provide a reasonable expectation that depleting B cells would be therapeutically beneficial in treating MS.

It is further noted that the observation by Genain and Hauser that the marmoset model shares in common with humans an acute from of demyelination does not constitute a "teaching away" for several reasons. First, Genain and Hauser do not teach that "MS involves only acute demyelination" as asserted by Applicant. Instead, they point out that this aspect, present in both humans and marmosets, is an aspect of pathology missing in many murine models. Genain and Hauser clearly teach MS involves more than acute demyelination (e.g., summarized in the Abstract on page 187).

Applicant also calls into question the Examiner's comment that Biozzi AB/H mice were "known in the art" to develop chronic-relapsing, rather than acute, EAE. The relevant statement of record was:

> "The Examiner notes that the Biozzi AB/H mice, which are the model system used by Turk et al., were known in the art to develop chronic-relapsing, rather than acute, EAE; and further notes that Biozzi AB/H (i.e., Biozzi AntiBody/High) mice were known in the art to be more susceptible to EAE induction than Biozzi AB/L (i.e., Biozzi AntiBody/Low) mice, *as referenced in the teachings of Turk et al. at column 9, lines 45-51*." Paper No. 10., emphasis added.

Thus the Examiner's comment was not based upon personal knowledge, but rather was made based upon the teachings and references provided by Turk et al.

Applicant also repeatedly asserts that the Examiner has provided no evidence that the information provided by Genain and Hauser and cited by the Examiner was information generally known or available to one of ordinary skill in the art.

Applicant's attention is called to the fact that the teachings of Genain and Hauser used in the rejection of record are in a "review" (see header on page 187 of reference).

It is further noted that the Review by Genain and Hauser provides ample review of the state of the art and the various benefits and limitations with respect to the different animal models and forms of EAE (chronic-relapsing, etc.).

Applicant's comments regarding anti-MOG antibodies are acknowledged. However, it is unclear how the specificity of the antibodies is in any way relevant to the conclusions the ordinary artisan would draw with respect to targeting B cells producing antibodies for depletion in view of the teachings of Genain and Hauser that antibody contributes to the pathology of MS. For the sake of argument it is noted that even if the pathogenic antibodies were limited in specificity to MOG, this does not change the fact that B cells are present in MS which produce antibody that contributes to disease pathology.

Finally, Applicant's assertion that no motivation to combine the references has been provided is believed to have been addressed in the body of the rejection of record, as reiterated supra.

Thus the Examiner maintains that, given the teachings of the references cited, the ordinary artisan at the time the invention was made would have found it obvious to deplete B cells in order to reduce the pathology of MS and in depleting B cells would have necessarily reduced a pro-MS response. Therefore, the Examiner maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the teachings of the references relied upon in the rejection set forth.

The rejection of record as applied to the amended and newly added claims is therefore maintained.

10. Applicant's amendment, filed 1/7/03, has obviated the previous rejection of claims 6-7 and 9 under 35 U.S.C. 103(a) as being unpatentable over either Hale et al (US Pat. No. 6,120,766, of record) or Aruffo et al (US Pat. No. 6,051,228, of record) in view of Turk et al. (US Pat. No. 5,958,409, or record).

Conclusion

11. No claim is allowed.

12. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
March 24, 2003

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
Tech Center 1600
3/24/03